Selection bias introduced by informative censoring in studies examining effects of vaccination in infancy

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Abstract

Background

Many studies have examined 'non-specific' vaccine effects on infant mortality: attention has been particularly drawn to diphtheria-tetanus-pertussis (DTP) vaccine, which has been proposed to be associated with an increased mortality risk. Both right and left censoring are common in such studies.

Method

We conducted simulation studies examining right censoring (at measles vaccination) and left censoring (by excluding early follow-up) in a variety of scenarios in which confounding was and was not present. We estimated both unadjusted and adjusted hazard ratios (HRs), averaged across simulations.

Results

We identified scenarios in which right-censoring at measles vaccination was informative and so introduced bias in the direction of a detrimental effect of DTP vaccine. In some, but not all, situations, adjusting for confounding by health status removed the bias caused by censoring. However, such adjustment will not always remove bias due to informative censoring: inverse probability weighting was required in one scenario. Bias due to left censoring arose when both health status and DTP vaccination were associated with mortality during the censored early follow up, and was in the direction of attenuating a beneficial effect of DTP on mortality. Such bias was more severe when the effect of DTP changed over time.

Conclusions

Estimates of non-specific effects of vaccines may be biased by informative right or left censoring. Authors of studies estimating such effects should consider the potential for such bias, and use appropriate statistical approaches to control for it. Such approaches require measurement of prognostic factors that predict censoring.

Keywords: survival analysis, time-to-event data, censoring, selection bias, vaccine non-specific effects, DTP vaccine

Key messages

1. Censoring may introduce biases in the estimation of the non-specific effect of DTP vaccine
2. Censoring at measles vaccination may lead to biased estimates of DTP effect in both directions
3. Excluding early follow-up can be problematic if the vaccine effect varies over time
4. Use of DAGs is advised to decide which potential confounders need to be considered

Background

Some authors have suggested that receipt of Bacillus Calmette-Guérin (BCG) vaccine and measles vaccine (MV) are associated with reduced risks of mortality for reasons other than tuberculosis and measles, respectively. Conversely, receipt of diphtheria-tetanus-pertussis (DTP) vaccine is postulated to be associated with an increased risk of mortality beyond its effects on the diseases it targets.(1-7) Such effects of vaccines on mortality beyond those on the specific diseases against which the vaccines are targeted are often referred to as 'non-specific' or 'heterologous' vaccine effects. Since these vaccines are administered to a large proportion of the world's children, the potential impact of non-specific effects on infant mortality is substantial. Hence, much attention has been drawn to these effects, in particular the possibility of a deleterious effect of DTP.

In a systematic review that motivated the work presented here, we aimed to integrate information from primary studies (both randomized trials and observational studies) that analysed non-specific effects of BCG, DTP and measles vaccines on all-cause mortality in children up to five years.(8) The findings appeared to concur with the claims summarized in the previous paragraph: most studies indicated that receipt of BCG and MV were associated with lower mortality and receipt of DTP was associated with higher mortality. However, most of the retrieved studies were observational studies and results were variable across studies, particularly for DTP. Poorly-controlled or uncontrolled confounding and various types of information bias have been suggested as alternative explanations for some of the findings.(9) In addition, most of these studies reported on time-to-event data, raising the possibility of biases being introduced by the phenomenon known as *censoring*.

Time-to-event data, also known as survival data, provide information about both the occurrence of an event and the time of its occurrence. The target in survival analysis is to follow up each subject from the starting point until the event of interest is observed. Follow-up is said to be censored when the information about the event time is incomplete.(10-12) The most commonly occurring type of censoring is right censoring, where follow-up ends before the event is observed. In contrast,

observations are said to be left censored if follow-up starts after the time of onset of risk, such as the time at which an intervention was received (sometimes referred to as 'time zero'). If participants' censoring times are associated with their time to event, then censoring is said to be informative and will lead to bias.(13) If participants' censoring times are statistically independent of their time to event, then censoring is said to be non-informative, and does not lead to bias.

The vaccination sequence currently advocated by the WHO, displayed in Figure 1, recommends that BCG be administered soon after birth, three DTP doses at ages 6, 10 and 14 weeks, and measles vaccine between ages 9 and 12 months.(14) To isolate the effect of DTP from that of BCG and measles vaccines, some analyses included in our review involved left-censoring (children were included in the analysis only from a time point after most DTP vaccinations had taken place)(15, 16) and some involved right censoring (follow-up was censored on receipt of measles vaccine).(17-21)

FIGURE 1 HERE

In this paper we examine the potential impact of these two types of censoring on the results of studies examining non-specific effects of vaccines. We focus on estimating non-specific effects of DTP vaccine, which were the most inconsistent and controversial estimates across studies in our systematic review. For simplicity, we focus on administration of the first DTP dose. We start by explaining how right censoring and left censoring may lead to bias by considering directed acyclic graphs (DAGs), which aim to represent causal relationships between variables and provide a framework for thinking about bias. We then present simulation studies that quantify the potential for bias, using plausible values for effects of vaccination on mortality and of health status as a potential confounder of this relationship.

Right censoring

Right censoring arises when the event of interest is not observed within the period of follow-up covered by the study. It may occur, for example, because the period of follow-up is short relative to the probability of the event occurring, due to competing outcomes (e.g. death in studies looking at

non-fatal outcomes) or due to loss to follow-up. Several studies examining non-specific effects of DTP vaccine censored children on receipt of measles vaccine.(18-22) Such censoring aims to avoid any effect of MV on infant mortality biasing the estimated effect of DTP. However, vaccinated children may be more likely to receive further vaccinations, for reasons including socio-economic status, distance to vaccination centre, residence in areas targeted by vaccination campaigns, and health status.(20, 23) Thus, DTP-vaccinated children may be more likely to receive measles vaccine as well.

The DAGs displayed in Figure 2 display possible relationships between DTP, MV, death (D) and a single potential confounder to represent health status (H). These are simplifications of the true situation, for the purposes of explaining the concepts. In reality there will be many variables, both measured and unmeasured, that influence vaccine uptake and mortality. Arrows between variables indicate the direction of cause and effect. All DAGs include an arrow from DTP to MV to reflect the assumption that receipt of DTP influences the probability of receiving MV, and a second arrow from H to D to reflect the assumption that health status influences death. Except for Figure 2E, in which DTP influences D via its effect on H, the absence of any paths from DTP or MV to D in these DAGs reflects the situation in which there are no causal effects of DTP or MV on death. Censoring at (conditioning on) MV is represented by the box around MV. The theory of causal inference determines that censoring on a variable that is a common effect of (caused by) two other variables induces an association between those variables in the uncensored participants.(13) Thus, censoring on MV changes the association between DTP and H in Figure 2C, 2D and 2E.

FIGURE 2 HERE

In Figures 2A and 2B, censoring at MV is not expected to bias the estimated effect of DTP. In Figure 2A there is no confounding (H does not influence the probability of receiving DTP or MV), so that censoring at MV does not induce any association between DTP and H, or between DTP and D. However, healthy infants may be more likely to be vaccinated than frail infants (23, 24) and this is

126 depicted in Figure 2B, where H confounds the association between DTP and D. Because MV is only
127 related to H and D through DTP, censoring at MV does not change the association between DTP and
128 death. Therefore, censoring is non-informative in both these scenarios.

129 Figure 2C and Figure 2D display situations in which H confounds the association between MV and D.
130 In each figure, MV is a common effect ('collider') of H and DTP, with the consequence that censoring
131 at MV will change the association between DTP and H (and hence between DTP and D) in uncensored
132 individuals. Therefore, censoring is informative in these scenarios. In Figure 2C censoring at MV
133 induces an association between DTP and D that is not present in the whole sample.

134 In Figures 2B to 2D, differences in the risk of death for vaccinated and unvaccinated children arise only
135 because health status H influences the probability of vaccination. Therefore, adjusting for H is
136 expected to remove the bias due to the confounding. In Figure 2E, by contrast, DTP affects the risk of
137 death via its effect on H, before measles vaccination (H is on the causal path from DTP to D). Therefore,
138 adjusting for H will bias the estimated effect of DTP on D towards the null.(13)

139

140 ## Left censoring

141 *Left censoring* ('left truncation') occurs when a period of follow-up after the start of intervention or
142 exposure starts is omitted from the analysis, typically because of delayed entry of the participants into
143 the study.(25) In most applications, an individual with left-truncated follow-up will only be included in
144 the analysis if he or she did not experience the outcome of interest during the missing follow-up
145 period. For some observational studies of the effect of DTP on infant mortality in our systematic
146 review, children were included in the analysis only from a time point after most DTP vaccinations had
147 taken place, thus excluding early follow-up after receipt of the vaccine for some children.(15, 16)

148 In a randomized trial, follow-up of participants starts at the time of allocation to the different
149 interventions, even if this includes a period before the intervention is actually implemented. Left

censoring (excluding early follow-up) in a randomized trial would generally be regarded as inappropriate because it discards follow up time and outcome events subsequent to randomization. By contrast, the absence of a clear time at which interventions were allocated means that left censoring often occurs in observational (non-randomized) studies of interventions. Left censoring will introduce bias in the estimated effect of an intervention if early events that are excluded by the left censoring are influenced by both the intervention and by other prognostic factors.(26) For example, Figure 3 depicts a situation in which children's health status H influences their risk of death D but is not associated with DTP vaccination, which also influences D. The left censoring implies that early deaths occurring before time point 1 (D_1) are excluded from the analysis. Because such deaths are common effects of both DTP and H (e.g. D is a collider), the censoring induces an association between DTP and H during the later period, and hence the effect of DTP on later death occurring between time points 1 and 2 (D_2) is confounded by H.

FIGURE 3 HERE

Left censoring is also problematic when the effect of intervention changes over time, for example when the proportional hazards assumption (that the intervention rate ratio is constant during follow-up) is violated. This includes situations where the effect of the vaccine is lower during the first period (e.g. full protective immunity is achieved one month after vaccination) and the opposite (e.g. vaccine efficacy declines with time since vaccination). In such scenarios, exclusion of early events will mean that the estimated intervention hazard ratio (HR) differs from the hazard ratio averaged over the whole time since the start of intervention, as would be estimated in a randomized trial. For example, a proportional hazards assumption would imply that the DTP HR is the same from DTP vaccination to time point 1 as from time point 1 to time point 2. Exclusion of events up to time point 1 means that the estimated DTP HR only reflects the effect of DTP during the interval between time points 1 and 2.

Simulation studies

We conducted Monte Carlo simulation studies to examine the potential influence of right and left censoring when estimating the effect of DTP on death, using HRs as effect measures. In both studies, we simulated cohorts of 1,000 children and generated lifetimes within a range of plausible values in deprived countries, according to infant mortality rates collected by UNICEF over the last six decades.(27). We scheduled administration of BCG, DTP (one dose) and measles vaccines at 0, 1.5 and 12 months, respectively. We set the probabilities of receiving each vaccine according to information reported from studies conducted in various countries.(1, 3, 6, 28, 29) To ensure simulation errors below 0.01 in all scenarios, 20,000 replicas were simulated for each condition,(30) and the effect estimates for each condition were defined as the arithmetic mean of the HRs obtained across replicas. All simulations were undertaken using R (v3.3.3)(31), with Cox regression models for HRs performed using the survival package.(32)

We defined children's health status by setting 30% of children as 'frail' and the other 70% as 'healthy'. Healthy children had lifetimes generated from a Weibull distribution with values of 1 and 15 for the shape and scale parameters, respectively. These correspond to a median lifetime of 13.9 years, with first and third quartiles of 4.3 and 20.8 years and a proportion of deaths before 5 years slightly above 0.28. Frail children had rates of death four times greater than healthy children, throughout follow-up. This was achieved by using Weibull distribution scale parameter 3.75.(10) We used the same strategy in the scenarios where a vaccine effect was introduced.

Right censoring simulation

We conducted simulations corresponding to the scenarios depicted in Figures 2A to 2E, by setting conditions with no confounding as well as with confounding at DTP vaccination, at MV, or both. In different scenarios, the probability of vaccination with DTP was influenced or not by health status H, while probabilities of MV were influenced by H or by prior receipt of DTP. We present the vaccination probabilities in Table 1.

TABLE 1 HERE

In scenarios 2A to 2D DTP vaccination did not influence D (causal HR=1), while in scenario E DTP reduced death rates (causal HR=0.5). The effect of DTP on death between 1.5 and 60 months was estimated both with and without censoring at measles vaccination, and both with and without adjustment for H. Follow-up was censored at age 60 months. For scenario E, we performed an additional analysis in which we corrected bias due to left censoring by estimating the probability of remaining uncensored based on H and DTP, and weighting the analysis based on the inverse of these probabilities.

Left censoring simulation

For this simulation study, both frail and healthy children had a probability of DTP vaccination of 0.5, ignoring other vaccination events. We defined effects of DTP vaccine on death from 0-6 months (early effect) and from 7-12 months (late effect). We considered large (HR=0.5) and small (HR=0.8) effects: and the combination of two values and two follow-up periods resulted in four different scenarios: (A) HR=0.5 throughout follow-up; (B) larger early effect (HR=0.5) and smaller late effect (HR=0.8); (C) smaller early effect (HR=0.8) and larger late effect (HR=0.5); and (D) HR=0.8 throughout follow-up. The effect of DTP on death after 12 months of follow-up, was estimated using both the complete follow-up period (uncensored) and excluding the first 6 months of follow-up (left censoring). It is pertinent to note here that effect measures such as odds ratios and hazard ratios are 'non-collapsible': even in the absence of confounding the conditional odds ratios within strata (e.g. healthy and frail children) are further from the null than marginal (overall) odds ratio. This property implies that, even in the absence of confounding and selection bias, when odds ratios and hazard ratios are used to estimate an association across strata the average of the within-stratum (conditional) estimates will not match the value of a single estimate across strata (marginal estimate).

Results of simulation studies

Table 2 shows results of the right censoring simulations. Average HRs were close to 1.0 (true causal effect) in the unconfounded scenario 2A, in which censoring was not informative. When confounding at DTP vaccination was introduced (scenario 2B), the average unadjusted HR, either with or without right censoring, suggested a beneficial effect of DTP vaccine (HR approximately 0.54). For scenarios 2C and 2D, censoring at MV is informative. For scenario 2C, the analysis without censoring at MV yielded an average unadjusted HR close to one, whereas the analysis censoring at MV estimated DTP to be harmful (HR=1.324). For scenario 2D, in which H confounds the effects of both DTP and MV, the unadjusted HRs suggested that DTP reduced mortality, but the informative censoring attenuated this beneficial effect towards the null.

TABLE 2 HERE

For scenarios 2B to 2D, average HRs for DTP were close to 1.0 (the true causal effect) after adjusting for health status H. This is because adjusting for H controls the confounding, and also blocks the backdoor path from H to DTP that is introduced by right censoring on MV. By contrast, adjusting for H did not correct the bias caused by informative censoring in scenario 2E. In this scenario there is no confounding, so that the unadjusted analysis without right censoring is unbiased (HR=0.5). Right censoring at MV yields a biased unadjusted HR of 0.66. Adjusting for H, which is on the causal pathway from DTP to D, introduced bias in the uncensored analysis (HR=0.536) and did not completely remove the bias in the censored analysis (HR=0.553). In this scenario an analysis that is weighted by the inverse probabilities of remaining uncensored is required for unbiased estimation of the effect of DTP vaccine in the presence of right censoring (13): the average HR from analyses employing this approach was 0.496.

TABLE 3 HERE

Results from the left censoring simulation are presented in Table 3. In scenarios A and D, the effect of DTP on D is constant over time. The adjusted analyses in these scenarios (both with and without left censoring) yielded estimates that are close to the true HR. The average unadjusted HRs in the uncensored analysis (0.521 and 0.818 for true HRs 0.5 and 0.8, respectively) are closer to the null than the true early and late HRs. These differences are *not* due to bias – they arise because the simulation analyses were stratified within time period and because the 'non-collapsibility' of HRs implies that, in the absence of confounding, 'marginal' HR averaged across strata are closer to the null than 'conditional' HR within strata.(11, 13) In the presence of left censoring, the unadjusted HR were further biased towards the null (average HRs 0.539 and 0.829 for true HRs 0.5 and 0.8, respectively), because the left censoring induces an association between H and DTP).

In scenarios B and C, where the true HR varies over time, the results in the absence of censoring were an average of the true early and late HR, with the unadjusted estimates closer to the null because of the non-collapsibility of the HR. In the presence of left-censoring, the adjusted HR was closer to the true late HR, while the unadjusted HR was biased towards the null (compared with the true late HR) because the left censoring induces an association between H and DTP.

Discussion

In the absence of evidence from randomized trials, cohort studies comparing vaccinated with unvaccinated children provide an opportunity to study 'non-specific' effects of vaccines. Confounding, together with different forms of selection and information biases, have been suggested as possible explanations for inconsistent findings from studies of such effects.(9, 33) Statistical analyses examining non-specific vaccine effects may be subject to both right and left censoring that arises because investigators wish to focus on a single vaccine within the WHO-recommended vaccination sequence. We used simulated data to explore the impact of censoring at measles vaccination (right censoring) and exclusion of early follow-up (left censoring) on estimates of the effect of DTP vaccine, which has been found to increase infant mortality in some studies.(8) Analyses of these simulated data

show that both left and right censoring may bias estimates of non-specific vaccine effects. In some circumstances, such bias may be adjusted for by controlling for prognostic factors (such as children's underlying health status) that predict censoring. However, conventional adjustment using regression models does not necessarily correct bias due to left or right censoring, even if the whole set of confounding factors can be identified and measured (which is unlikely in practice). This is because predictors of censoring may also be on the causal pathway from vaccination to the outcome (as is the case in our scenario E), in which case adjustment through regression modelling is not appropriate to deal with the bias caused by censoring (alternative methods such as inverse probability weighting are required). Although many of our simulations assumed no effect of DTP vaccine on mortality, our findings apply in the presence of an effect (in either direction). This is because the distortion created by selection bias may induce an apparent vaccine effect when none is present, or may alter the estimated magnitude (and even the direction) of a vaccine effect when it is present.

Unadjusted estimates of the effect of DTP that censor children on receipt of measles vaccine may be biased towards a beneficial DTP vaccine if healthier children are more likely to receive DTP vaccine. However, if healthier children are more likely to receive measles vaccine, then the right censoring will bias estimated effects towards a harmful effect of DTP vaccine. We showed that such bias can be removed by fully adjusting for the confounding but, importantly, this depends on perfectly measuring prognostic variables such as health status (defined as a binary variable in our simulations) that predict receipt of measles vaccine. Further, such adjustment does not remove bias if such variables are on the causal pathway from DTP vaccination to measles vaccination. We found that in such a situation, weighting by the inverse of the probability of remaining uncensored would remove the bias.(13)

The potential for bias due to left censoring (exclusion of early follow up) has received little consideration in studies of non-specific vaccine effects. Our simulation study examining left censoring showed that, even in the absence of confounding of the effect of DTP on mortality, left censoring will lead to bias if a prognostic factor such as health status predicts both early and later deaths. Such bias

could be controlled by adjusting for such prognostic factors, provided that they had been perfectly measured. Left censoring also implies that estimated vaccine effects are based only on later follow up, so that they cannot be compared with the effects that would be observed in a randomized trial (in which participants are analysed from the time of assignment to intervention groups. In practice, left censoring is best avoided by starting follow-up for each individual at the time at which they are vaccinated, or eligible for vaccination but not vaccinated. Interpretation of our simulation study of left censoring was complicated by the 'non-collapsibility' of the HR, which is reflected in the difference between unadjusted and adjusted estimates, even in the absence of confounding. Non-collapsibility has been documented for odds ratios (13) as well as effect measures that are used for time-to-event data.(11)

Our findings have important implications for studies assessing non-specific effects of vaccines. In our recent systematic review, all studies examining the effect of DTP on all-cause mortality in childhood were observational.(34) It is plausible that frail children are less likely to receive vaccination than healthy children.(23, 24) Furthermore, recent research suggests that a substantial part of the population in West African countries – where most studies showing a deleterious effect for DTP have been conducted – are suspicious about the effects of vaccines (35, 36): this might differentially affect vaccination coverage among healthy and frail infants. Thus, censoring at measles vaccination, which is presented in some studies as the primary analysis (or even the only analysis reported), may lead to bias through the mechanisms examined in our studies of right censoring. Future such studies should consider whether prognostic factors (such as health status in our simulations) may predict both measles vaccination and mortality. If this is the case, such factors should be measured and their effects adjusted for using appropriate statistical methods. Similarly, the potential for bias due to left censoring (exclusion of early follow up) should be considered. Directed acyclic graphs (DAGs) can be useful to clarify assumptions about censoring mechanisms, and choice of appropriate statistical analyses.

Our results do not necessarily explain the findings of an adverse effect of DTP vaccine on mortality reported by a number of studies that were included in our systematic review.(8) The biases observed in our simulation studies are probably too small to account fully for the inconsistent effect estimates reported in this field. Future empirical studies are warranted to clarify aspects such as the magnitude and direction of the non-specific effects of DTP and the impact of the vaccination sequence. Given the practical challenges of identifying and perfectly measuring all relevant confounders in this context, randomized controlled trials examining the non-specific effects of DTP vaccine (where ethically acceptable) have the potential to provide valuable insights. Nonetheless, randomized trials may suffer from selection bias due to right censoring, if the risk of the outcome differs between participants who were and were not lost to follow up.

To conclude, the scenarios and results that we presented in this paper illustrate the potential for a type of bias that has been insufficiently considered to date. Authors of studies estimating non-specific vaccine effects should consider the potential for selection biases introduced by right and left censoring and, if possible, use appropriate statistical approaches to control for them. Such approaches require measurement of prognostic factors that predict censoring.

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Tables

Table 1. Probabilities of vaccination set for the right censoring simulation

Scenario	Health	P(DTP|BCG)	P(DTP|no BCG)	P(MV|DTP)	P(MV|no DTP)
A. No confounding	Frail	0.85	0.7	0.7	0.4
	Healthy	0.85	0.7	0.7	0.4
B. Confounding DTP	Frail	0.65	0.5	0.7	0.4
	Healthy	0.95	0.8	0.7	0.4
C. Confounding MV	Frail	0.85	0.7	0.3	0.1
	Healthy	0.85	0.7	0.9	0.5
D. Confounding DTP & MV	Frail	0.65	0.5	0.3	0.1
	Healthy	0.95	0.8	0.9	0.5
DTP effect on death	Frail	0.85	0.7	0.3	0.1
	Healthy	0.85	0.7	0.9	0.5

Risk of death within the first 5 years of life was 0.28 for healthy children and 0.74 for frail children, respectively. Probability of BCG vaccination was 0.85 for both frail and healthy children across all scenarios

444 Table 2. Average hazard ratios (HR) for the effect of DTP on mortality, in the right censoring
445 simulation studies.

Scenario	True HR	Unadjusted HR		Adjusted HR	
		No censoring	Right censoring*	No censoring	Right censoring*
A - Unconfounded	1.0	1.003	1.004	1.002	1.004
B – Confounding at DTP	1.0	0.539	0.540	1.002	1.003
C – Confounding at MV	1.0	1.004	1.324	1.003	1.002
D – Confounding at DTP and MV	1.0	0.539	0.728	1.001	1.001
E – Prior effect of DTP	0.5	0.506	0.660	0.536	0.553

446 DTP: diphtheria-tetanus-pertussis vaccine; MV: measles vaccine;
447 *Right censoring is at the time of MV.

448

Table 3. Average hazard ratios (HR) for the effect of DTP on mortality, in the left censoring simulation studies.

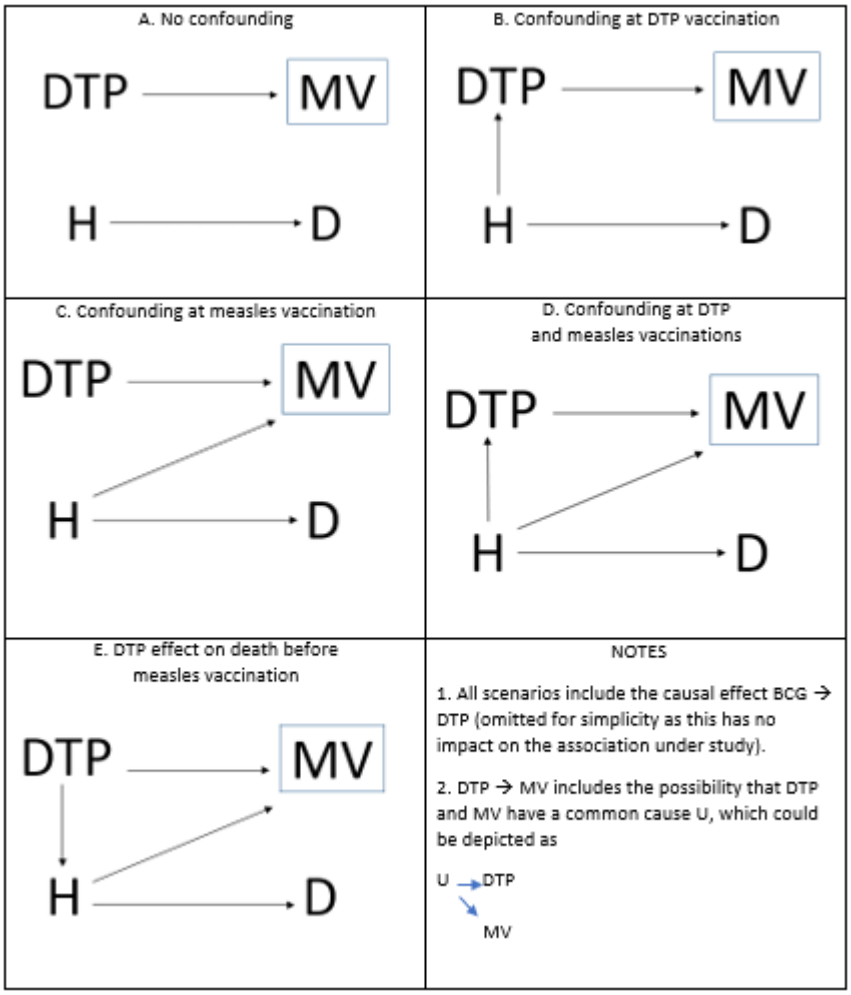
Scenario	True early HR	True late HR	Unadjusted HR		Adjusted HR	
			No censoring	Left censoring*	No censoring	Left censoring*
A	0.5	0.5	0.521	0.539	0.505	0.506
B	0.5	0.8	0.662	0.845	0.644	0.809
C	0.8	0.5	0.678	0.527	0.668	0.505
D	0.8	0.8	0.818	0.829	0.808	0.809

*Left censoring is at 6 months (the end of the early period after DTP vaccination)

Figures

Figure 1. Vaccination sequence recommended by WHO at present

Footnote: BCG: Bacillus Calmette-Guérin; DTP: diphtheria-tetanus-pertussis (1st, 2nd and 3rd dose); MV: measles vaccine



462

463 Figure 2. Non-informative and informative right censoring using DAGs

464 Footnote: DTP: diphtheria-tetanus-pertussis (1st dose); MV: measles vaccine; H: health status; D:
465 death; Boxes indicate selection (censoring) of follow-up time according to the boxed variable

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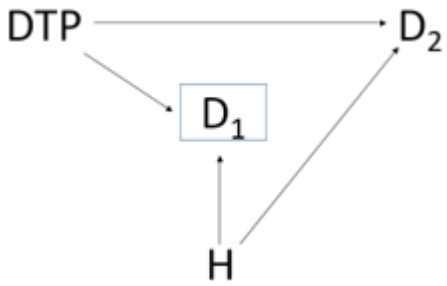

Figure 3. DAG for left censoring

Footnote: DTP: diphtheria-tetanus-pertussis (1st dose); H: health status; D_1: death at time point 1; D_2: death at time point 2